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# Stimulus-Responsive Contact Lens for IOP Measurement or Temperature-Triggered Drug Release

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**Purpose:** Continuous monitoring of elevated intraocular pressure and timely drug delivery for successful treatment of glaucoma are necessary to reduce intraocular pressure (IOP), which shows wide variations across the circadian pattern and in response to medication. This in vivo study presents a new contact lens-based method of optical IOP measurement or temperature-triggered drug elution.

**Methods:** A contact lens with moiré patterns of concentric circles measures the changes in eyeball diameter of a rabbit glaucoma model due to changes in IOP by superimposing a camera-captured image onto the micro pattern of the contact lens with a computer-assisted virtual reference image. Drug elution from the nanoporous bicontinuous microemulsion contact lens (BME-CL) into the eye of the rabbit was triggered by a temperature-responsive nanogel drug carrier.

**Results:** The moiré pattern change on the contact lens was proportional to the IOP increase in the rabbit eye either ex vivo or in vivo and was also correlated with imaging-based alterations in the anterior chamber angle at a range of IOP values (3–40 mm Hg). The cumulative drug absorbed reached as high as 10.6 µg/mL aqueous humor until 7 days after wearing the BME-CL, and a 33% decrease in IOP was observed at 3 hours after drug elution.

**Conclusions:** The results suggest that continuous measurement and treatment of elevated IOP are feasible using moiré pattern-inscribed and thermosensitive drug-eluting contact lenses, respectively.

**Translational Relevance:** Pressure-sensing or thermosensitive contact lenses enable monitoring IOP or drug release triggered by body temperature for the treatment of glaucoma patients.

## Introduction

The contact lens is a suitable wearable smart device for either sensing ocular physicochemical parameters[1–4] (intraocular pressure, temperature, biomolecules in tears) or delivering drugs for the treatment of various ocular diseases.[5] Elevated intraocular pressure (IOP) is a major risk factor for the development and/or progression of glaucoma,[6,7] and timely drug delivery is necessary to prevent retinal tissue damage by reducing IOP. Contact lens-based continuous monitoring of IOP is necessary for successful treatment of glaucoma because patients can have a wide variation of IOP across the circadian pattern.[8] Current contact lens-based electromechanical measurements of IOP require integration of power batteries and strain-gauge circuits, including signal transmission, in addition to external receivers, resulting in either expensive devices or limited accessible places for successful data acquisition.[9] A study of optical monitoring of IOP used moiré patterns generated from two overlap-

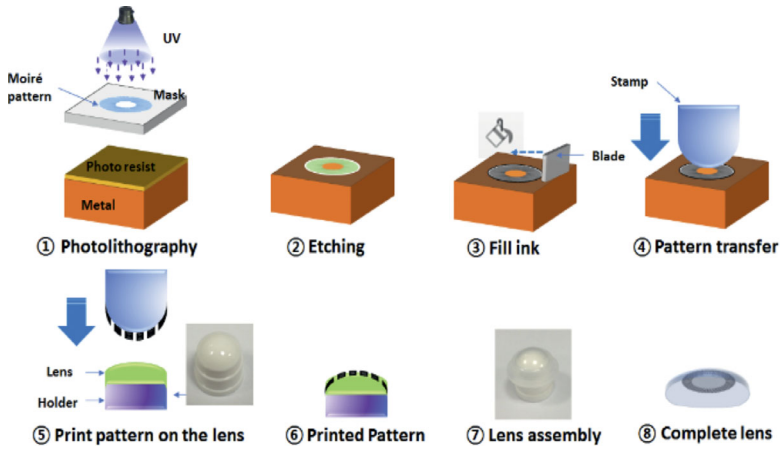


**Figure 1.** Schematic of the processing steps for imprinting the moiré pattern.

ping contact lenses,[10] which was inconvenient for the wearers due to the thickness of the two lenses.

Compared to eye drops, which have a low delivery efficiency, contact lens-based drug delivery is a more effective method to deliver drugs by direct contact with the cornea. Stimulus-triggered drug release from contact lenses is an emerging technique to deliver therapeutic payloads on demand while preventing drug loss due to premature elution from the lenses during shipping and storage.[11,12] It is desirable to investigate drug-eluting effects using an in situ acute glaucoma model that allows quick evaluation of the effective therapeutic doses, especially considering the poor correlation of in vitro drug release studies with in vivo drug efficacy. In this study, we present a feasibility study of optical IOP measurement by generating changes in a moiré pattern superimposed on contact lenses with virtual reference images and body temperature-triggered, drug-eluting contact lenses in a glaucoma rabbit model.

# Methods

## Moiré Pattern Imprinting of Contact Lenses

A moiré pattern is an interference pattern produced by overlaying similar but slightly offset templates.[13] A simple example is obtained by taking two identical ruled transparent sheets of plastic, superposing them, and rotating one about its center as the other is held fixed (Supplementary Material SI-1). We tried to print a concentric moiré pattern in a contact lens. The contact lens was fabricated with concentric patterns (100 µm in width and gap) by a contact lens manufacturer (Dreamcon, Changwon, Korea) using conventional pattern transfer printing that provided a minimum resolution of approximately 50 µm as depicted in Figure 1. A photomask with photoresist was applied to a metal surface and then overlaid with a photomask bearing a moiré pattern generated with computer-aided design (CAD) software. The material was exposed to ultraviolet (UV) light and dissolved in a developer solution, leaving the microscale pattern etched into the photoresist. Ink filled the patterned line, and a stamp transferred the ink to the surface.

## Preparation of a Temperature-Sensitive, Drug-Loaded Nanogel and Incorporation into Contact Lenses

We prepared drug-eluting bicontinuous microemulsion nanoporous contact lenses (BME-CLs) using a polymerizable surfactant, as described previously.[12] Briefly, the polymerizable surfactant Silmer A008-UP (Siltech Corporation, East York, Ontario, Canada) was mixed with a prepared aqueous phase liquid (water and hydroxyethylmethacrylate [HEMA]) and nonaqueous phase liquid (ethylene glycol dimethylacrylate and 3-[*tris*(trimethylsiloxy)silyl] propyl methacrylate). The mixed monomer was polymerized with a UV curing system at 250 to 450 nm for 15 minutes in a casting mold. Timolol-loaded thermosensitive poly(*N*-isopropylacrylamide) (PNIPAM), nanogels were prepared and loaded into the BME-CLs by using soaking combined with centrifugation.[12]

## Preparation of an Acute Glaucoma Model

Ten albino rabbits (New Zealand white) of mixed sex with body weights ranging from 2.5 to 3.0 kg were used. The animals were kept under standardized conditions and given tap water and food ad libitum. The

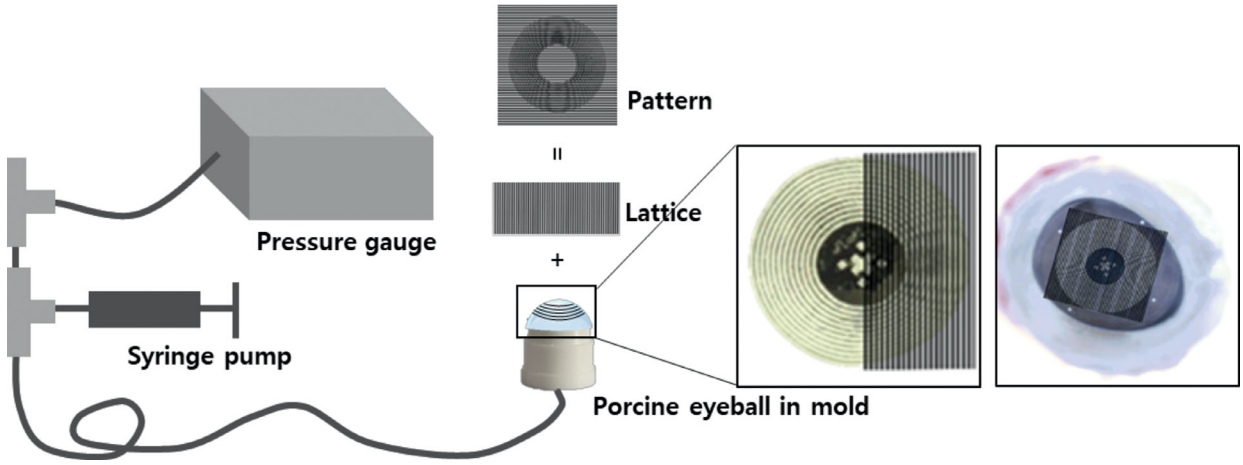


**Figure 2.** Experimental setup for generating and measuring the IOP-responsive moiré pattern in contact lenses placed on an ex vivo enucleated porcine eyeball.

experimental procedures for animals were approved by the Institutional Animal Care and Use Committee of Daegu Catholic University and conformed to the principles of animal treatment described in the Statement for Use of Animals in Ophthalmology and Vision Research of the Association for Research in Vision and Ophthalmology. The rabbits were anesthetized with ketamine hydrochloride 35 mg/kg and xylazine (Rompun; Bayer, Leverkusen, Germany) 5 mg/kg intramuscularly. Tetracaine hydrochloride eyedrops (Alcaine 0.5%; Alcon, Geneva, Switzerland) were used for local anesthesia. The aqueous humor was withdrawn to 50 µL, and then 50 µL of Healon (Johnson & Johnson Vision, Jacksonville, FL) was injected using a 31-gauge needle and a 0.3-ml syringe through the anterior chamber at the superior corneal limbus in a manner that created a self-sealing wound.[14,15]

The IOP of the rabbit eye was elevated by injection of either Healon or a balanced salt solution (BSS) into the corneal limbus and checked with a tonometer (Icare TONOVET; Icare Finland Oy, Vantaa, Finland) and ultrasound biomicroscopy (UBM) (Tomey Corporation, Aichi, Japan). UBM imaging was performed to measure changes in the self-defined anterior chamber angle which may reflect IOP-induced morphological changes.

## Generating a Moiré Pattern with a Contact Lens in an Ex Vivo Porcine Eye

The experimental setup included an image capture unit, a syringe pump, a pressure sensor, and a latex balloon eyeball model or an enucleated ex vivo porcine eyeball, as shown in Figure 2. Conventional HEMA-based contact lenses were placed on an enucleated porcine eyeball. Because BSS physiological saline was injected continuously into the eyeball using an infusion pump, the moiré pattern on the contact lens was captured by a conventional camera. The captured image was overlaid with the computer-generated vertical strip as a virtual reference image to form a superimposed moiré pattern. To extract IOP data from overlaid moiré patterns, the relative changes in the image pattern were converted into waveform signals over a pixel-by-pixel histogram of gradient (HOG) algorithm using MATLAB (MathWorks, Natick, MA), in which pixel intensity information was converted into gradient information. Then, waveform analysis by Fourier transform provided an approach to extract data on IOP changes.

## In Vivo IOP Measurement by Sensing Change in the Moiré Pattern

Rabbits with acute glaucoma were prepared by either a continuous injection of BSS or a single injection of Healon into the corneal limbus and checked by pressure gauge or tonometer, respectively, as shown in Figure 3. UBM imaging was performed to measure the change in the anterior chamber angle according to the Healon-induced IOP change. The contact lens was securely placed on the rabbit cornea, and the moiré pattern on the contact lens was captured by a conventional camera. Generation of a virtual image of the superimposed moiré pattern and further waveform analysis to withdraw information on the IOP change were performed as described in the ex vivo case.

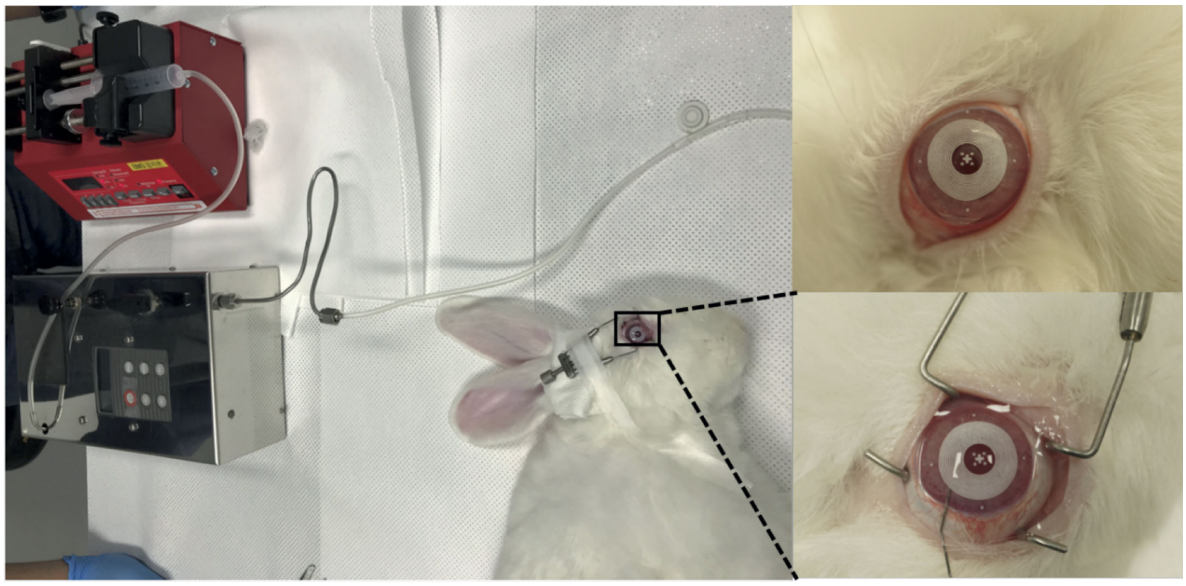

**Figure 3.** In vivo measurement of IOP in a rabbit glaucoma model.

### Measurement of Drug Elution from the Contact Lens

Drug-loaded contact lenses were placed on the left cornea of a rabbit. To prevent drying of the contact lens on the surface of the eye, slight partial tarsorrhaphy was performed using surgical tape.[16] In all animals, the left eye was used for the experiments, and the right eye was used as an untreated control. At predetermined time periods, the eyes of anesthetized rabbits were examined and sampled to study the drug flux into the eye. To accomplish this, we slid the contact lens to the side of the cornea, and a 31-gauge needle was inserted through the corneal limbus in a manner that created a self-sealing wound. Aqueous humor samples were quantified by UV–visible spectroscopy absorption measurements at 294 nm.[17]

## Results and Discussion

### Imprinting a High-Resolution Pattern on a Contact Lens

Concentric circle patterns were printed with a resolution of 100 µm/100 µm (width/valley) on conventional HEMA-based contact lenses. Prior to transfer of the sensing centric pattern, the contact lens was coated with white base material to improve the contrast of the moiré pattern. Then, a sensing pattern was formed on the contact lens as shown in Figure 4 to visualize the pressure change as a moiré effect.

### Glaucoma Rabbit Model

An acute glaucoma rabbit model was generated by either continuous infusion of BSS using an infusion pump or a single injection of Healon into the corneal limbus. Elevated IOP, checked by pressure gauge or tonometer, was in the range of 3 to 40 mm Hg. When the IOP was elevated from 10 mm Hg to 35 mm Hg, the anterior chamber angle was increased by 8°, as shown in Figure 5. UBM images clearly showed alterations in morphology beneath the cornea, suggesting an effect of elevated IOP.

### Moiré Pattern Generation for IOP Measurement Ex Vivo

Instead of using two contact lenses to generate a moiré pattern,[10] we generated another moiré pattern in a virtual second layer using CAD software (Supplementary Material SI-2), thus eliminating the need for additional contact lenses. A contact lens fabricated with a moiré pattern of concentric circles measures the changes in eyeball diameter according to intraocular pressure. The moiré effect to monitor IOP change is formed by superimposing a virtual reference image onto the micro pattern of the contact lens. After alignment and skew calibration of concentric images in the contact lens, the moiré image can be analyzed by HOG and Fourier transformation to extract information on pressure changes using MATLAB software. We used Fourier series transformation to determine the displacement from the moiré patterns generated

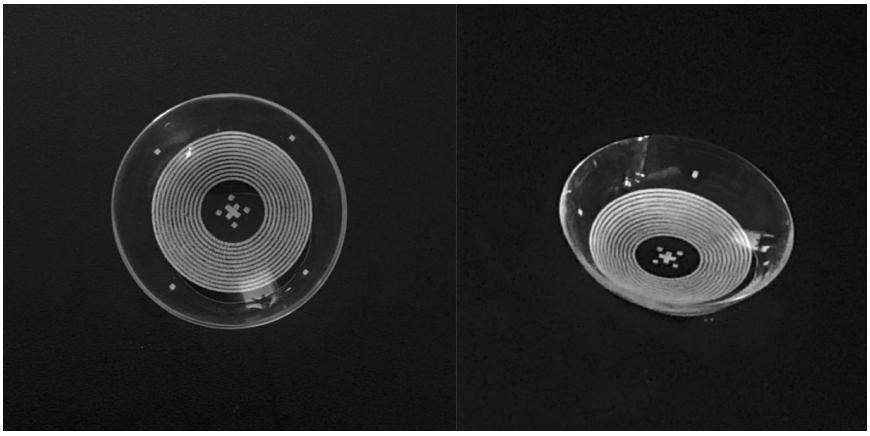

**Figure 4.** Manufactured moiré pattern-imprinted contact lens.

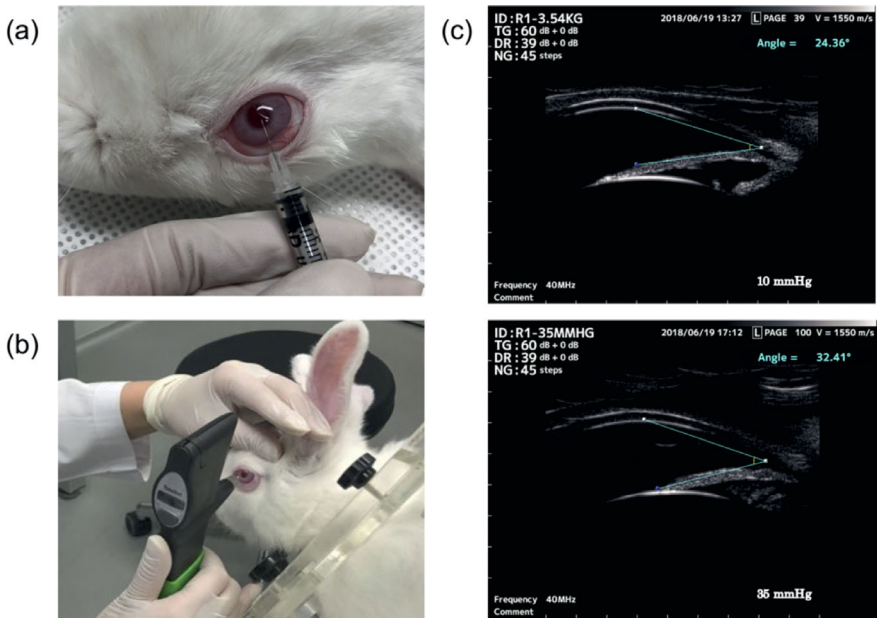


**Figure 5.** (a) Injection syringe for extraction of aqueous humor and insertion of Healon. (b) Measurement of intraocular pressure in a rabbit by tonometer. (c) Ultrasound biomicroscopy images of self-defined anterior chamber angle changes as depicted in one rabbit eye; upper panel: normal eye (10 mm Hg), lower panel: acute glaucoma model eye (35 mm Hg).

by overlapping two gratings of very high frequency. An algorithm based on the computational method was developed using MATLAB software. The graphically generated grating moiré pattern was first transformed into the polar coordinate plane. We employed a HOG algorithm for extracting features of the image that converts the pixel intensity information into oriented gradient information as a one-dimensional HOG feature vector. Gradients have both magnitude and direction.

The HOG algorithm is comprised of six stages. First, luminosity values are extracted from the gradient values. Second, the gradient of each pixel relative to its surrounding pixels is calculated. The third stage involves calculation of the magnitude of each $x$- and $y$-gradient pair and addition of the resultants to the relevant cell bin. Then, blocks are generated by locally normalizing groups to improve the invariance for illumination and shadowing. Collation of the blocks over the full detection window is carried out in the fifth stage to produce HOG descriptors. Finally, MATLAB receives the HOG features and multiplies with its set weights to achieve the moiré pattern image as a signal. The moiré pattern was considered as a waveform and

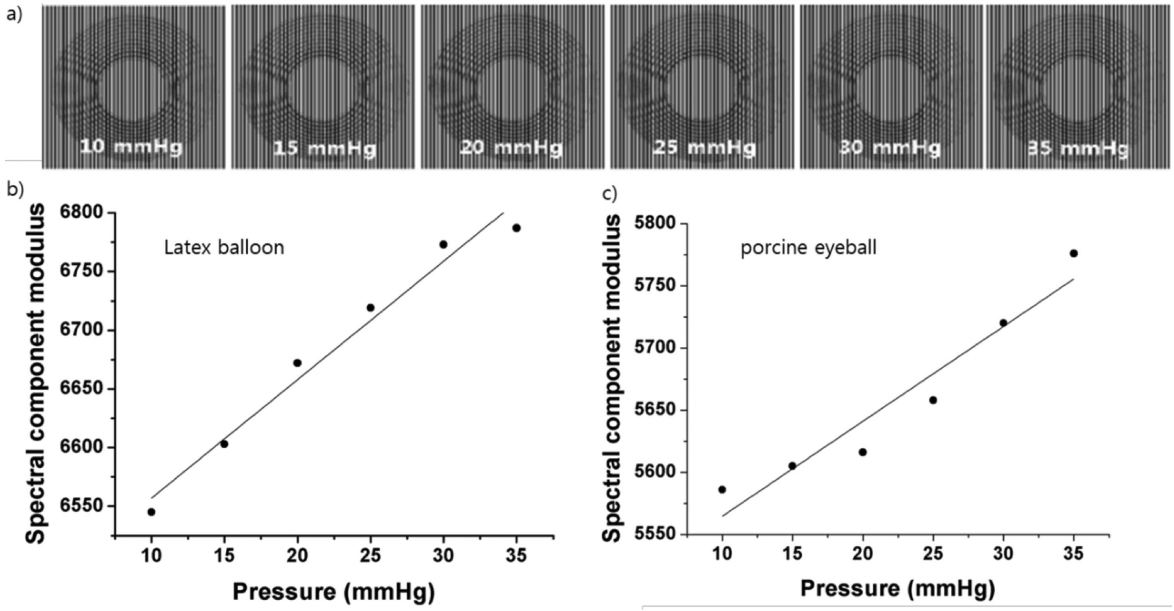


**Figure 6.** Moiré patterns according to induced IOP (a). Graphs show the correlation between the moiré pattern change and induced IOP in the latex balloon model (b) and porcine eyeball (c).

analyzed by fast Fourier transform in which the amplitude of the fundamental frequency was used to represent the feature of HOG. The frequency that contains the spectral component of highest power is known as the fundamental frequency. We found that the values were proportional to the applied pressure in the porcine eyeball as well as a latex balloon, as shown in Figure 6. The pressure ranged from 10 to 35 mm Hg, and linear fitting showed a strong correlation between the amplitude of the fast Fourier transform and the applied pressure, with $R^2 > 0.92$ in both cases.

## IOP Measurement In Vivo

As the IOP increased by injecting Healon, the moiré pattern on the contact lens could be substantially changed; however, it was difficult to recognize these changes with the contact lens image alone, as shown in the second column of Figure 7. Superimposed moiré patterns produced substantial change more clearly, as shown in the right-most column of Figure 7. Measurements of the moiré pattern changes and UBM angles according to the pressure applied demonstrated a notable correlation, as shown in Figure 7. Such a correlation was also observed between the IOP and the moiré pattern change in a wider range of IOPs that were induced via continuous BSS water injection (1–30 mm Hg), as shown in Figure 8. Application of this optical measurement of IOP requires a camera to capture moiré patterns consecutively for potential continuous IOP monitoring in patients and computer-based imaging analysis to obtain information on IOP changes. Mispositioning of lens or eye movement may translate shifted moiré patterns that were distinguished from the patterns by the IOP-mediated relative offset. This kind of distortion could be ruled out by the estimation of correlated IOP change. This optical technique is potentially useful for continuous or repeated monitoring of IOP in clinical settings as long as the contact lenses have sufficient oxygen permeability and mechanical stability.

## Temperature-Sensitive, Drug-Loaded Nanogel and Incorporation into a Contact Lens

Combined soaking with centrifugation facilitated the incorporation of timolol-loaded thermosensitive PNIPAM nanogels into nanoporous BME-CLs (100–250 nm). The nanogel (30 mg) carrying the timolol (1.79 mg/mL) was dissolved in 15 ml of ethanol prior to being loaded into BME-CLs by centrifugation (3000 rpm, 3 hours) and soaking (69 hours) at 4°C. Then, contact lenses were soaked in 100 mL of phosphate-buffered saline to extract the ethanol at 4°C while removing the adsorbed drug on the surface of the contact lens. The nanogel particles were retained in the contact lenses during the solvent exchange because they are larger than ethanol. As a result, the initial volume of timolol loaded in the contact lenses was 507.23 ± 50.30 µg. Retention of nanogel with a

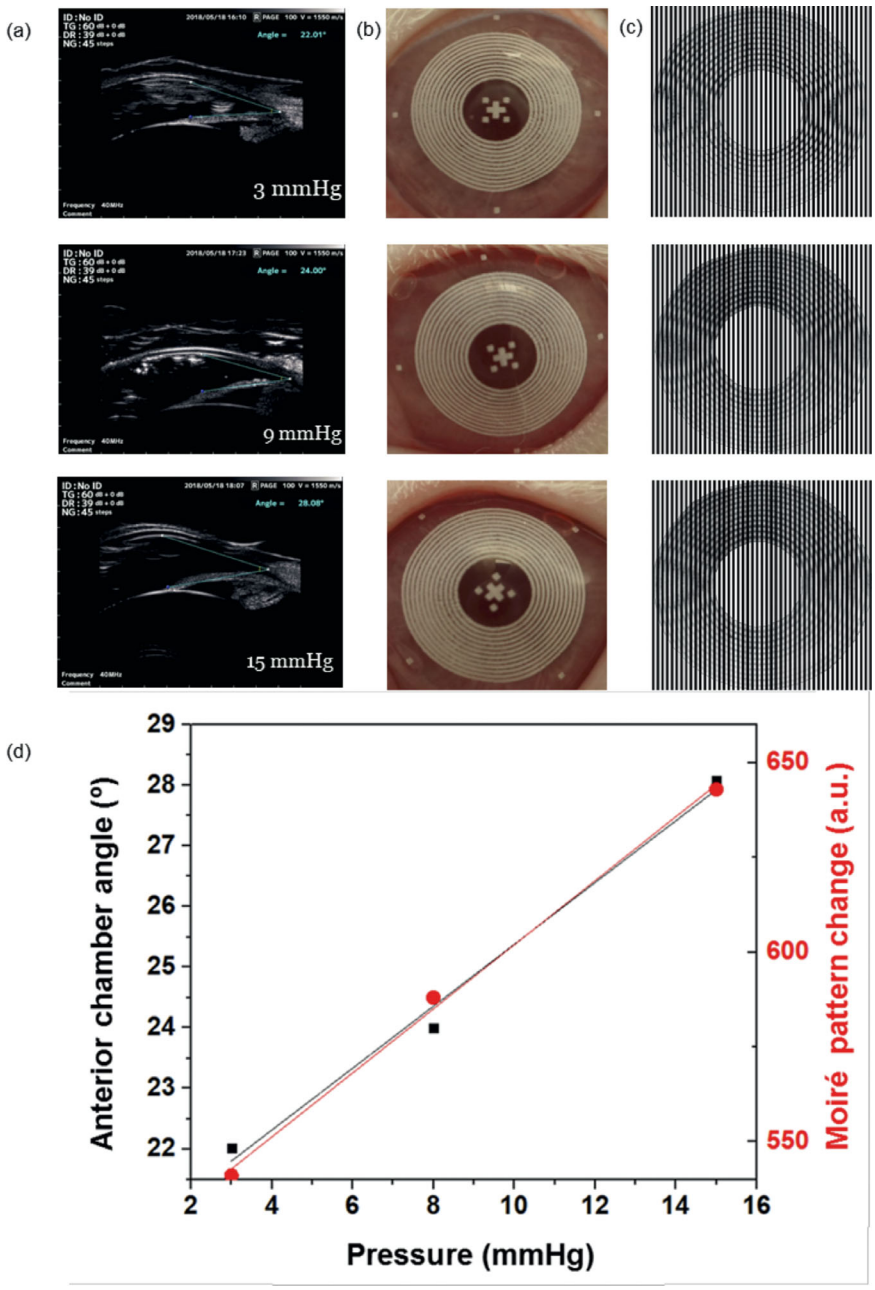


**Figure 7.** Moiré pattern-based IOP measurement in a rabbit with glaucoma induced by Healon injection. (a) Morphological changes detected by ultrasound biomicroscopy. (b) Moiré pattern-inscribed contact lenses and the induced changes in IOP. (c) Superimposed moiré patterns with virtual reference images representing IOP changes implicitly. (d) Changes in superimposed moiré patterns correlated with IOP changes and morphological changes around the cornea.

size of 50 nm did not affect optical transparency by the absence of scattering or mechanical stability of the contact lenses, as described previously.[12] Based on the relationship between drug release and initial loading volume reported in previous study,[12] only one initial drug loading dose was used in this work to test drug elution and therapeutic efficacy in a rabbit model.

## In Vivo Drug Release and Bioavailability Studies

To confirm drug release and bioavailability, we quantitatively assessed timolol concentrations in extracted aqueous humor as the absorbed dose achieved by continuous wearing of contact lenses. Contact lenses were worn continuously by rabbits, and

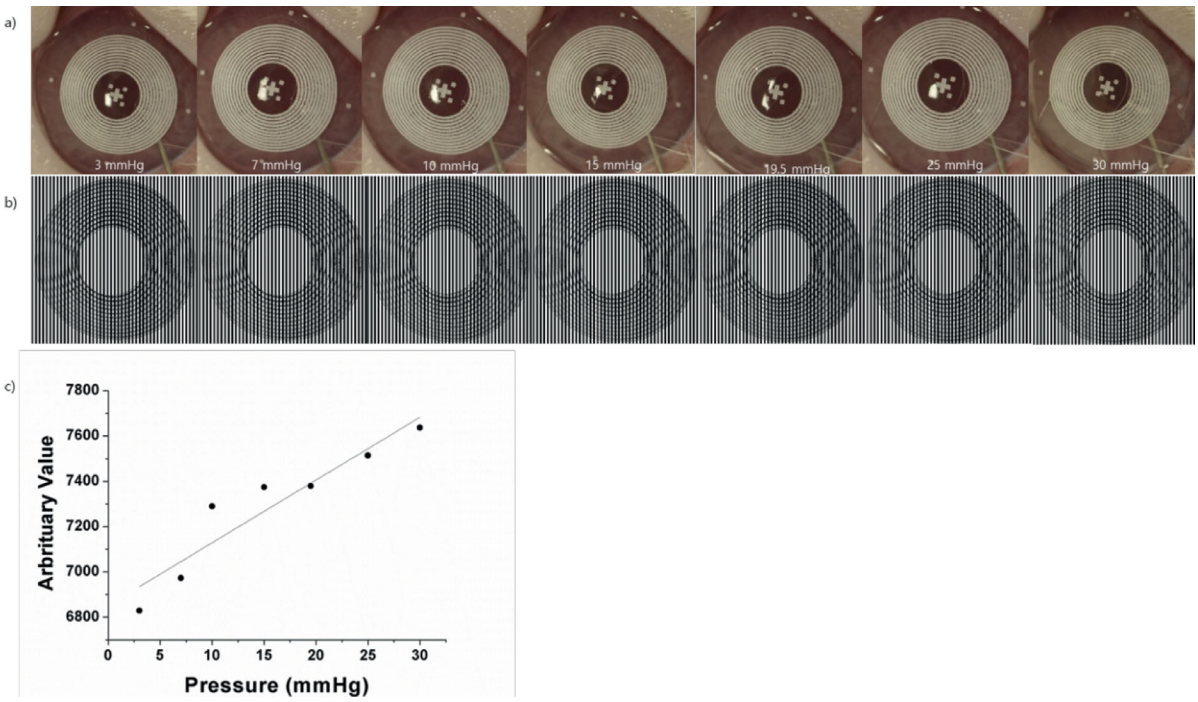


**Figure 8.** Moiré pattern-based IOP measurement in rabbits with glaucoma induced by continuous BSS water injection. (a) Moiré pattern-inscribed contact lenses and the induced changes in IOP. (b) Superimposed moiré patterns with virtual reference images representing IOP changes implicitly. (c) Changes in superimposed moiré patterns correlated with the IOP changes.

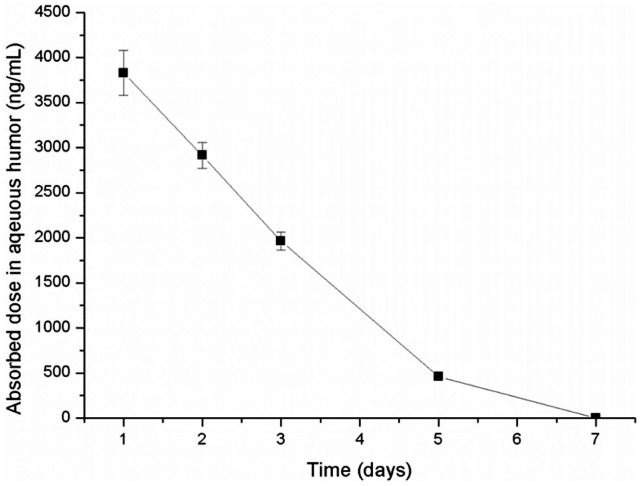


**Figure 9.** Concentrations of timolol maleate absorbed in the aqueous humor in rabbits wearing drug-eluting contact lenses.

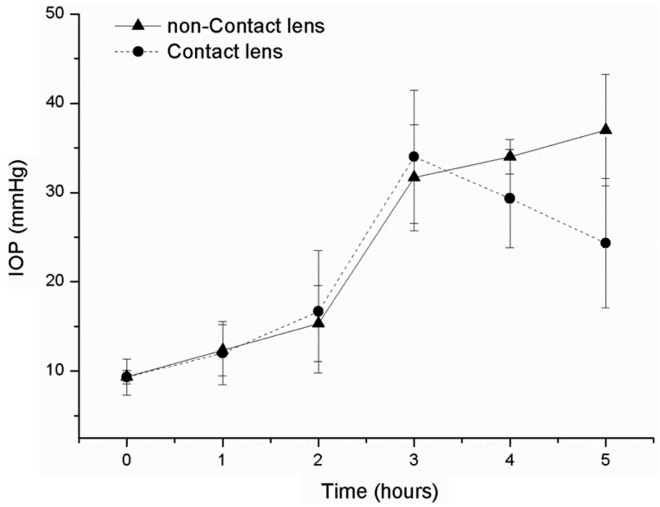


**Figure 10.** IOP changes in untreated control rabbits compared with rabbits wearing contact lenses.

aqueous humor was sampled every day for 1 week. The drug absorbed up to 7 days after wearing contact lenses, as shown in Figure 9. The fraction of the cumulative dose absorbed in the aqueous humor was estimated to be 10.6 μg/mL for 7 days. Considering a physiological aqueous volume of more than 250 μl, the potential absorbed dose retained in the aqueous humor would be approximately 2.65 μg. The drug distribution in the whole area of the ocular environment was not available. More drugs would be distributed in tissues other than the aqueous humor after release from BME-CLs. Therefore, it would be expected that actual total drug release from contact lenses would be larger than estimated in the aqueous humor due to unavailable drug distribution data for other tissues, including drainage of the aqueous humor.

### Effect of Drug-Eluting Contact Lenses in a Rabbit Glaucoma Model

We compared IOP changes between the untreated control group and the contact lens-wearing group in the acute glaucoma model induced by Healon injection. IOP decreased significantly by 33% in the group wearing contact lenses compared with the untreated control ($p < 0.01$) within 2 hours as shown in Figure 10. Because the drug begins to release only after being triggered by body temperature, the results showed that the initial (within 1 hour after wearing the contact lens) an absorbed dose of 4.3 µg/mL in the aqueous humor effectively induced a decrease in IOP. Because the Healon-induced acute glaucoma model retains elevated IOP only for 1 day, continuous monitoring of the therapeutic effect of drug elution was not possible. However, the reduction of IOP upon drug elution suggests continuous therapeutic effects for the glaucoma model due to wearing the BME-CLs.

## Conclusions

Moiré patterns imprinted on a single contact lens could measure IOP changes in a rabbit acute glaucoma model when combined with a computer-generated virtual image, eliminating the necessity of overlaying a second contact lens to produce IOP-proportional moiré patterns. This achievement may lead to the realization of optical measurement of IOP in clinical settings without inconveniencing the patient. Body temperature-triggered drug elution from nanoporous BME-CLs had a therapeutic effect, as evidenced by the rapid reduction in IOP after the contact lenses were worn in an acute glaucoma model. Importantly, the development of smart contact lenses for on-demand drug release to sense IOP could be feasible in the future.

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* S-HL and K-SS contributed equally to this article.

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